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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,067	10/06/2003	Ronald R. Breaker	23239-202 CIP CON	9946
30623 7590 02/21/2007 MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C. ONE FINANCIAL CENTER BOSTON, MA 02111			EXAMINER SHIN, DANA H	
			ART UNIT 1635	PAPER NUMBER

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/21/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/680,067	Applicant(s) BREAKER, RONALD R.	
	Examiner Dana Shin	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 December 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21-45 is/are pending in the application.
- 4a) Of the above claim(s) 31-33 and 41-43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21-30, 34-40, 44 and 45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) ☐ Notice of Informal Patent Application |
| 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>8-16-04, 8-30-04, 11-16-04</u> . | 6) ☐ Other: _____ |

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DETAILED ACTION

Election/Restrictions

Claims 31-33 and 41-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 29, 2006.

Status of Claims

Claims 21-45 are pending; claims 31-33 and 41-43 are withdrawn. Accordingly, claims 21-30, 34-40, and 44-45 are currently under examination on the merits.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119 and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

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This application is claiming the benefit of prior-filed nonprovisional application No. 09/331,809 under 35 U.S.C. 120, 121, or 365(c). Copendency between the current application and the prior application is required. Since the applications are not copending, the benefit claim to the prior-filed nonprovisional application is improper. Applicant is required to delete the reference to the prior-filed application from the first sentence(s) of the specification, or the application data sheet, depending on where the reference was originally submitted, unless applicant can establish copendency between the applications.

Further, the disclosure of the prior-filed applications, Application Nos. 60/033,684, 60/055,039, PCT/US97/24158, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. None of the prior-filed applications disclose the instantly claimed subject matter, a polynucleotide of mixed RNA and DNA nucleotide composition.

Accordingly, the benefit of priority is granted so far as the filing date of application No. 09/849,069, which is May 4, 2001. If applicant believes that the claimed subject matter in the instant case is adequately described and supported in the manner provided by the first paragraph of 35 U.S.C. 112, applicant is encouraged to point out the particulars in response to this Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 21-30, 34-40, and 44-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and /or chemical properties, functional characteristics, structure/function correlation, or any combination thereof.

In the instant case, the breadth of claims 21-30, 34-40, and 44-45 embraces any and all genera of polynucleotides of mixed RNA and DNA comprising an allosteric site and an enzyme domain, wherein a chemical effector changes the cleavage function/configuration of the polynucleotides. As broadly claimed, the specification does not clearly allow persons of ordinary skill in the art to recognize that the inventors invented what is claimed in the claims. The instant specification provides no representative number of species of the claimed polynucleotides of mixed RNA and DNA as it does not contain any disclosure of complete or partial structure of the broadly claimed mixed RNA and DNA allosteric polynucleotides nor does it provide any structure/function correlation of the claimed polynucleotides. The specification merely states that allosteric polynucleotides of the invention are comprised of any natural, recombinant, or synthetic RNA, DNA and mixtures of RNA and DNA. See page 16, lines 22-23. Except for this mere statement in the specification, the instantly claimed allosteric polynucleotides comprising mixed RNA and DNA are not further elaborated as part of the claimed invention. Accordingly, in the absence of sufficient recitation of distinguishing

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identifying characteristics, the specification does not provide adequate written description of the claimed genus. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making it. The compound itself is required. See *Fiers v. Revel*, 984 F.2d 1164, 1168, 25 USPQ2d 1601,1604-05 (Fed. Cir. 1993).

See also *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991), which clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (see page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed” (see page 1116).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 21, 23, and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Perreault et al. (*Nature*, 1990, 344:565-567).

The claims are drawn to a polynucleotide of mixed RNA and DNA comprising an allosteric site and an enzyme domain, wherein an effector changes the cleavage function or configuration of the polynucleotides, wherein the effector is a metal ion (claims 21, 23) or nucleosides/nucleotides (claim 27).

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The term "allosteric site" is interpreted to mean an allosteric effector binding site, in view of the specification (pages 15-16).

Perreault et al. teach a mixed DNA and RNA composition with catalytic activity, which conducts cleavage reactions in the presence of Mg^{2+} and Pb^{2+} (pages 565-566 and Figures 1-3). They teach that the mixed DNA and RNA composition also mediates ribozyme-catalyzed cleavage when contacted by an oligonucleotide substrate (page 566 and Figure 1b and 3).

Since the polynucleotide of mixed RNA and DNA of Perreault et al. catalyzes self-cleavage upon contacting the metal ions or an oligonucleotide substrate (effector), one skilled in the art can infer that the polynucleotide of Perreault et al. must have an allosteric site on which the effectors could bind and an enzyme domain which catalyzes cleavage. Further, since the polynucleotide of mixed RNA and DNA of Perreault et al. meets the structural requirements set forth in claim 23, the rate of catalysis of the enzyme domain would inherently be modulated in a reversible manner as claimed in claim 23, absent evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

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evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 21-30, 34-40, and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al. (*Nucleic Acids Research*, 1998, 26:4214-4221) in view of Soukup et al. (*Current Opinion in Structural Biology*, 2000, 10:318-325) and Eckstein et al. (US 5,672,695).

The claims are drawn to polynucleotides of mixed RNA and DNA and biosensors comprising the polynucleotides, wherein the polynucleotides have three stem components and the allosteric site and the enzyme domain are spatially distinct, wherein stem II forms the allosteric site, wherein the rate of catalysis of the enzyme domain is measured by observing enzyme self cleavage or substrate cleavage and occurs 6 minutes or less or 1 minute or less after interaction with a chemical effector, wherein the chemical effector is nucleosides/nucleotides, and a biosensor comprising the allosteric polynucleotides comprising modified nucleotides and is attached to a solid support.

Tang et al. teach that an aptamer-ribozyme construct functions as an allosteric ribozyme, whose aptamer domain undergoes conformational change upon ligand binding, which in turn reduces catalytic activity of the adjacent ribozyme domain having three stems (page 4214; Figures 1 and 3). They teach that the allosteric site and ribozyme domain can be designed in a spatially distinct manner so that stem II forms an allosteric site and the two functional domains (allosteric site and enzyme domain) can operate without steric interference (pages 4214, 4217-4220). They teach that allosteric behavior of an aptamer-ribozyme construct can be mediated

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through small effector molecules, including flavine mononucleotide (pages 4214 and 4220).

They teach that the thermodynamic and kinetic parameters determine the maximization of the 'on' and 'off' states and the rate of interconversion between states (page 4220). They teach that the catalytic activity as well as receptor-ligand forming function of the aptamer-ribozyme construct is incorporated into new allosteric ribozymes or even deoxyribozymes that are regulated by small effector molecules. They further teach that with new design strategies, it is possible to assess whether "enzymes made of RNA and DNA" participate in more complicated catalytic networks and use them as controllable therapeutic enzymes or for industrial applications (page 4220). Tang et al. do not teach the rate of catalysis of the enzyme domain or a biosensor comprising allosteric polynucleotide comprising mixed DNA and RNA comprising modified nucleotides, wherein the polynucleotides is attached to a solid support.

Soukup et al. teach that allosteric nucleic acid catalysts are used as therapeutic agents or as sensors of their cognate effector compounds (page 318). They teach that nucleic acid catalysts exhibit allosteric transitions in response to effector binding and are capable of rapidly converting from an 'inactive' to an 'active' state or vice versa upon addition of ligand, which depends on the conformational changes that accompany effector binding (page 319). They teach that an oligonucleotides as effectors. See Figure 1(e) on page 320. They also teach various catalytic rates of different allosteric ribozymes in Table 1, page 321. They teach that allosteric nucleic acid catalysts are employed to detect the presence or concentration of specific effectors in which the catalytic event is coupled to amplification, accessory reporters, or microchip technologies (page 323).

Eckstein et al. teach that RNA molecules with catalytic activity (ribozymes) comprising at least one modified nucleoside have enhanced stability against chemical and enzymatical degradation (column 2, lines 44-49, 55-65; column 3, lines 37-59).

It would have been obvious to one of ordinary skill in the art to make an allosteric polynucleotide of mixed RNA and DNA in view of the teachings of the prior art at the time the invention was made. One of ordinary skill in the art would have been motivated to make an aptamer-ribozyme construct having an allosteric site and an enzyme domain that are spatially distinct wherein the construct have three distinct stem structures as taught by Tang et al. The skilled artisan would have had a reasonable expectation of success of modifying the aptamer-ribozyme construct of Tang et al. to comprise mixed DNA and RNA (e.g., aptamer comprising DNA and ribozyme comprising RNA) to use in various therapeutic and industrial applications as taught by Tang et al. (see page 4220). Further, it would have been obvious to the skilled artisan to make a biosensor comprising the allosteric aptamer(DNA)-ribozyme(RNA) construct of Tang et al., because Soukup et al. expressly teach that such allosteric nucleic acid catalysts are used as biosensors that are incorporated into microchip technologies (see page 323). The skilled artisan would have been motivated to make such biosensors comprising allosteric mixed RNA-DNA catalysts with a reasonable expectation of success because Soukup et al. expressly teach that allosteric nucleic acid catalysts are employed to detect the presence or concentration of specific effectors. The skilled artisan would have been further motivated to incorporate nucleotide modifications in the biosensors comprising the allosteric mixed RNA-DNA catalysts with a reasonable expectation of success because it was well known in the art at the time the instant invention was made that nucleotide modifications in ribozymes help to increase stability against

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degradation as taught by Eckstein et al. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time the application was filed.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

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Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 21-27, 29-30, 34-40, and 44-45 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19 and 23-24 of U.S. Patent No. US 6,630,306 B1. Although the conflicting claims are not identical, they are not patentably distinct from each other for the reasons set forth below:

The disclosure of the patent teaches that “Allosteric, polynucleotides of the invention are comprised of any natural, recombinant, or synthetic RNA, DNA, and mixtures of RNA and DNA”. See column 9, lines 42-44. That is, the instantly claimed polynucleotide of mixed RNA and DNA nucleotide composition is an obvious variant of the claimed DNA polynucleotide and RNA polynucleotide of the US 6,630,306 patent.

The court in *Vogel* recognized “that it is most difficult, if not meaningless, to try to say what is or is not an obvious variation of a claim,” but that one can judge whether or not the invention claimed in an application is an obvious variation of an embodiment disclosed in the patent which provides support for the patent claim. According to the court, one must first “determine how much of the patent disclosure pertains to the invention claimed in the patent” because only “[t]his portion of the specification supports the patent claims and may be considered.” The court pointed out that “this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103 since only the disclosure of the invention claimed in the patent may be examined.” See *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

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In view of the foregoing, the examined application claims, claims 21-27, 29-30, 34-40, and 44-45, are either anticipated by, or would have been obvious over, the reference claims of the US patent.

Conclusion

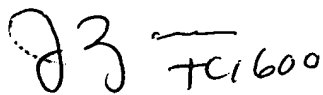
No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635


JANE ZARA, PH.D.
PRIMARY EXAMINER